

## Regulated Expansion of Lympho-hematopoietic Stem and Progenitor Cells from Human Embryonic Stem Cells (hESC)

### Grant Award Details

Regulated Expansion of Lympho-hematopoietic Stem and Progenitor Cells from Human Embryonic Stem Cells (hESC)

**Grant Type:** Comprehensive Grant

**Grant Number:** RC1-00108-B

**Investigator:**

**Name:** Gay Crooks  
**Institution:** University of California, Los Angeles  
**Type:** PI

**Human Stem Cell Use:** Embryonic Stem Cell

**Award Value:** \$1,653,416

**Status:** Closed

### Progress Reports

**Reporting Period:** Year 1

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**Reporting Period:** Year 3

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## Grant Application Details

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**Application Title:** Regulated Expansion of Lympho-hematopoietic Stem and Progenitor Cells from Human Embryonic Stem Cells (hESC)

**Public Abstract:** The clinical potential of human embryonic stem cells (hESC) for transplantation will be realized only when we can develop methods to control the process of tissue differentiation far more efficiently than is currently the case. From over 40 years of experience with adult stem cells, it is recognized that the growth of transplanted bone marrow is generated from the hematopoietic ("blood-forming") stem and progenitor cells present in the graft. Mature, differentiated cells that accompany the stem cells disappear rapidly after transplantation as they lack the ability to self renew. It is thus essential when designing clinical approaches that use tissue derived from hESC, to specifically target the production of stem and progenitors that will survive, proliferate and differentiate after transplantation. This proposal addresses three fundamental questions for the entire hESC field 1. Do hESC differentiate through the same pathways that exist in adult tissues, 2. How do the conditions in which hESC are initially derived from blastocysts affect their subsequent potential for generating tissue specific stem and progenitor cells, and 3. How can hESC differentiation be regulated to provide large numbers of tissue specific stem and progenitor cells able to engraft and differentiate long term? Studies of hematopoiesis in mice have provided the conceptual basis for the entire field of stem cell biology. However, fundamental biological and technical differences exist in both hematopoietic and embryonic stem cell biology between the murine and human species. Our group has chosen over the past 15 years to focus on the study of human hematopoietic stem cells and lymphoid (immune system) progenitors, more recently bringing these concepts and tools to study hematopoietic differentiation from hESC. In brief, our aims in this proposal are: 1. To understand the pathways along which the blood and immune system are generated from hESC, 2. To assess if the methods by which hESC are derived affect their capacity for hematopoiesis, and 3. To develop the means to expand hematopoietic stem cells derived from hESC. I believe that there are two broad reasons why these studies are important. First, as a pediatric bone marrow transplant physician, I am keenly aware that profound clinical problems remain for my patients. Matched stem cells from healthy donors are often unavailable and poor recovery of the immune system after transplantation results in an unacceptably high incidence of death and illness from infection. Second, as a stem cell biologist I recognize that the well established tools that can be applied specifically to hematopoietic development from hESC are uniquely able to answer some of the most fundamental questions about how hESC generate tissues and how we can best control the process. With these answers we will be able to tailor our approaches for differentiation to all tissue types and move the intriguing biology of hESC more rapidly and safely to the clinic.

**Statement of Benefit to California:**

The unique combination of pluripotentiality and unlimited capacity for proliferation have provoked hope that hESC will one day provide an inexhaustible source of tissue for transplantation and regeneration. Diseases that might be treated from such tissues affect millions of Californians and their families. However, the clinical potential of hESC for regenerative medicine will be realized only when the process of tissue specific differentiation is significantly more efficient and controlled than is currently the case.

This research proposal has two broad goals. The first is to explore some of the fundamental biologic questions about how individual human embryonic stem cells (hESC) are recruited into a specific pathway of tissue differentiation. Our approach to these questions will be to use the hematopoietic ("blood-forming") system as our model, as it is the best characterized tissue in terms of differentiation and offers a range of unique technical tools with which to study these questions rigorously. However, the fundamental concepts formed from these studies will have broad applicability to other types of tissues. By understanding these processes, the development of methods to translate hESC into production of other tissues such as islets, neural cells and cardiac muscle to the clinic will be more successful.

The second goal is to develop approaches to efficiently produce elements of the blood and immune system from hESC for use in transplantation of a variety of diseases. Hematopoietic Stem Cell Transplantation (HSCT, aka Bone Marrow Transplantation) is the most mature example of the clinical application of stem cells, representing a life saving procedure for leukemia, lymphoma, and many other types of blood and immune system diseases. Nonetheless, profound clinical problems remain for the HSCT field particularly in the allogeneic setting. These problems include lack of suitable, matched bone marrow donors for many patients and poor recovery of the immune system after transplantation leading to death and illness from infection in an unacceptably large number of patients. The possibility of producing large numbers of compatible hematopoietic stem and progenitor cells suitable for clinical transplantation presents an opportunity to fundamentally change clinical practice in the HSCT field.

All scientific findings and technical tools developed in this proposal will be made available to researchers throughout California, under the guidelines from the California Institute of Regenerative Medicine.

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